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THE ROLE OF ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN DIABETES

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Myocardial infarction (MI) and ischemic stroke comprise the leading causes of morbidity and mortality in patients with diabetes mellitus (DM).[1] Cardiovascular disease (CVD) results in fatalities more often in patients with concomitant DM than in those without DM.[2] Half of patients with DM die within one year after experiencing their first cardiac event.[2] Of these, half suffer sudden death and die before reaching the hospital.[2] The risk of a first MI in patients with DM is approximately equal to the risk in patients without DM who have suffered a previous MI.[3] These harrowing statistics further validate primary prevention of CVD— specifically MI and stroke—for the population with DM. Considering the approximately 25.8 million people in the United States with DM[4], safely and effectively preventing CVD is of critical importance and a crucial public health initiative in this population. Patients with DM have a two- to fourfold increased risk of both stroke and death from heart disease relative to the general population without DM matched for age and sex.[4] A 2004 review of cause of death of patients with DM aged at least 65 years revealed 68% and 16% of deaths were attributable to heart disease and stroke, respectively.[4]

The use of antiplatelet agents is well established for the secondary prevention of cardiovascular events in patients with DM.[5] However, the use of aspirin therapy for primary prevention of CVD is more controversial irrespective of DM diagnosis. The absolute risk of a cardiovascular event is approximately 10 times higher in those with established CVD versus those with risk factors but without overt CVD[6]; thus, the potential absolute benefits of aspirin are expected to be lower for primary than secondary prevention. The 2009 updated guidelines issued by the United States Preventative Services Task Force (USPSTF) recommended the use of aspirin in the primary prevention of CVD for all men 45 to 79 years old and women 55 to 79 years old so long as the risk of bleeding does not outweigh the potential benefit of preventing MI or ischemic stroke in men and women, respectively.[7] Importantly, USPSTF did not differentiate between patients with or without DM in their recommendations.[7]

In this review, guideline recommendations will be discussed in light of the most recent evidence of aspirin use in CVD primary prevention for patients with DM. Additional concerns when determining appropriateness of therapy will be addressed. Finally, the necessity for additional study will be established.

Currently Available Evidence

Early population-based studies, which utilized subgroup analyses of patients with DM, were underpowered to show a significant reduction in cardiovascular events with aspirin therapy. The Antithrombotic Trialists' (ATT)[6] collaborators pooled the results of six of these trials—Women's Health Study (WHS)[8], Primary Prevention Project (PPP)[9], Hypertension Optimal Treatment (HOT)[10],

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Thrombosis Prevention Trial (TPT)[11], Physicians' Health Study (PHS)[12], and British Medical Doctors (BMD)[13] (**Table 1**). Altogether, ATT combined the results from 95,000 patients at low-average risk of CVD to study serious vascular events (primary outcome) in long-term aspirin use versus control.[6] Approximately 4,000 (4.2%) of these patients had DM. Baseline characteristics varied widely including discrepancies in estimated 10-year coronary risk (range 5.4% to 33.5%).[8-13]

Aspirin therapy demonstrated a statistically significant 12% risk reduction over placebo in serious vascular events for the overall population in ATT (0.51% [aspirin] versus 0.57% [placebo] per year; RR 0.88; 95% CI 0.82 to 0.94; $p = 0.0001$).[6] This risk reduction was primarily attributable to the significant 23% relative decline in nonfatal MI (0.18% versus 0.23% per year; RR 0.77; 99% CI 0.67 to 0.89; $p < 0.0001$).[6] On the other hand, aspirin use did not significantly affect rates of coronary heart disease (CHD) mortality (0.11% versus 0.12% per year; RR 0.95; 99% CI 0.78 to 1.15; $p = 0.5$) or total stroke (0.20% versus 0.21% per year; RR 0.95; 95% CI 0.85 to 1.06; $p = 0.4$).[6]

Subgroup analysis revealed similar reductions in the relative risk of the major primary outcome when patients were stratified by DM diagnosis.[6] Despite this finding, the endpoint was significant in people without DM (RR 0.87; 95% CI 0.79 to 0.96) but nonsignificant in people with DM (RR 0.88; 95% CI 0.67 to 1.15) due to the reduced numbers of patients with DM and outcome events in this subgroup.[6]

Most of the evidence of aspirin effectiveness in patients with DM but without established CVD has arisen from two 2008 published trials: the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial[15] and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial.[16] Neither of these trials was without shortcomings, and each will be discussed separately in this review.

POPADAD investigated aspirin for primary prevention in 1,276 patients with DM aged 40 years or older with asymptomatic peripheral arterial disease (ankle brachial pressure index < 0.99).[15] Patients were randomly allocated to blinded treatment, based on a 2x2 factorial design, with aspirin (100 mg daily) plus antioxidant (n = 320), aspirin plus placebo (n = 318), antioxidant plus placebo (n = 320), or placebo plus placebo (n = 318).[15] POPADAD investigated two hierarchical composite primary endpoints: death from CHD or stroke, nonfatal MI or stroke, or above ankle amputation for critical limb ischemia; and death from CHD or stroke.[15] The study was underpowered to detect the originally planned 25% relative reduction in event rate due to slow recruitment and lower-than-expected number of outcomes.[15]

By the end of five years of follow-up, 50% of patients had stopped taking their assigned treatment.[15] Since no statistically significant difference was observed between the occurrence of reported adverse events between aspirin and non-aspirin groups, non-compliance was the most likely motive behind patient dropout.[15] The study employed intention-to-treat analysis to provide a more conservative estimate of risk reduction in the presence of this high drug discontinuation rate.[15] POPADAD authors found no evidence of an interaction between aspirin and antioxidant for either of the primary endpoints ($p = 0.88$ for the composite primary end point; $p = 0.95$ for death from CHD or stroke); as such, the researchers made comparisons between the two aspirin arms and the two placebo arms for evaluation of the efficacy of aspirin therapy.[15]

Overall, POPADAD found that aspirin was no more effective than placebo at preventing cardiovascular events in patients with DM and asymptomatic peripheral arterial disease.[15] The primary composite endpoint was not statistically significant in the aspirin group (116 events) versus the no aspirin group (117 events) (HR 0.98; 95% CI 0.76 to 1.26; $p = 0.86$).[15] Likewise, no significant difference in death from CHD or stroke was observed between groups (43 events for aspirin therapy versus 35 events for placebo; HR 1.23; 95% CI 0.79 to 1.93; $p = 0.36$).[15]

An open-label, randomized trial with blinded endpoint assessment, JPAD, studied the effect of low-dose aspirin on preventing CVD in type II DM patients aged 30 to 85 years.[16] Two thousand five hundred and thirty-nine patients were randomly assigned to treatment with aspirin (81mg or 100mg daily) (n = 1262) or placebo (n = 1277).[16] However, patients in the placebo group were permitted to use antiplatelet or antithrombotic therapy, including aspirin, as needed.[16] Six patients (0.5%) in the non-aspirin group took aspirin, and three patients (0.2%) took a different antiplatelet medication.[16] The primary end point was any atherosclerotic event—a composite of sudden death; death from coronary, cerebrovascular, and aortic causes; non-fatal acute MI; unstable angina; newly developed exertional angina; nonfatal stroke; TIA; or nonfatal aortic and peripheral vascular disease.[16]

The frequency of primary endpoint events in the aspirin group (68 events) was not statistically different compared with the placebo group (86 events; HR 0.80; 95% CI 0.58 to 1.10; $p = 0.16$).[16] A post-hoc subgroup analysis of patients aged 65 years or older (n = 719 in the aspirin group; n = 644 in the placebo group) found a statistically significant difference in the primary endpoint of atherosclerotic events (45 events in the aspirin group versus 59 events in the placebo group) favoring aspirin

Table 1 | Primary prevention trials of aspirin use in patients with DM.

Study (year)	PO-PADAD[15] (2008)	JPAD[16] (2008)	WHS[8a] (2005)	PPP[9a] (2001)	HOT[10ab] (1998)	TPT[11ab] (1998)	ETDRS[14] (1992)	PHS[12a] (1988)	BMD[13ab] (1988)
Design	DB, 2x2 (antioxidant vs. placebo), RCT	PROBE	DB, 2x2 (vitamin E vs. placebo), RCT	open-label, 2x2 (vitamin E vs. open-label control), RCT	DB, RCT with 3 competing BP regimens	DB, RCT with factorial treatment groups (warfarin vs. placebo)	DB, RCT	DB, 2x2 (carotene vs. placebo), RCT	open-label, RCT
Aspirin dose	100mg/ day	81mg or 100mg/ day	100mg every other day	100mg/ day	75mg/ day	75mg/ day	650mg/ day	325mg every other day	500mg/ day
Population	patients with DM and asymptomatic PAD	patients with type II DM	female health professionals	men and women with ≥1 risk factor(s) for CHD	men and women with DBP 100-115 mmHg	men with risk factors for CHD	patients with DM, retinopathy, and +/- CVD disease	male doctors	male doctors
Patients with DM (%)	1,276 (100%)	2,539 (100%)	1,027 (2.6%)	1,031 (22.9%)	1,501 (8.0%)	68 (1.3%)	3,711 (100%)	533 (2.4%)	101 (2.0%)
Mean age	60	65	54	64	61	57	NA	53	61
Country	Scotland	Japan	USA	Italy	Europe, N. & S. America, Asia	UK	USA	USA	UK
Mean follow-up (years)	6.7 (median)	4.4 (median)	10.1	3.7 (median)	3.8	6.7	5.0	5.0	5.6
Endpoint	1)composite endpoint[c]; 2)death from CHD or stroke	atherosclerotic events	composite of CV death, MI, or stroke	composite of CV death, MI, or stroke	MCE	MCE	all cause mortality	MI	MCE
Event rate (aspirin vs control)	1)116/638 vs. 117/638 (18.2% vs. 18.3%) 2)43/638 vs. 35/638 (6.7% vs 5.5%)	68/1262 vs. 86/1277 (5.4% vs. 6.7%)	58/533 vs. 62/494 (10.9% vs. 12.6%)	20/519 vs. 22/509 (3.9% vs. 4.3%)	21/752 vs. 27/749 (2.8% vs. 3.6%)	4/29 vs. 6/39 (13.8% vs. 15.4%)	340/1,856 vs. 366/1,855 (18.3% vs. 19.7%)	11/275 vs. 26/258 (4.0% vs. 10.1%)	13/69 vs. 6/32 (18.8% vs. 18.8%)
RR (95% CI)	1)0.98 (HR) (0.76-1.26) 2)1.23 (HR) (0.79-1.93)	0.80 (HR) (0.58-1.10)	0.90 (0.63-1.29)	0.90 (0.50-1.62)	0.77 (0.44-1.36)	0.90 (0.28-2.89)	0.90 (0.75-1.11 [99% CI])	0.39 (NA)	1.00 (0.42-2.40)

2x2 = 2x2 factorial design; **BMD** = British Medical Doctors; **BP** = blood pressure; **CHD** = coronary heart disease; **CI** = confidence interval; **CVD** = cardiovascular disease; **DB** = double blind; **DBP** = diastolic blood pressure; **DM** = diabetes mellitus; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **HOT =** Hypertension Optimal Treatment; **HR** = hazard ratio; **JPAD** = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes**; MCE** = major coronary event (CHD death, nonfatal MI, sudden death); **MI**= myocardial infarction; **NA** = not available; **PHS** = Physicians' Health Study; **POPADAD** = Prevention of Progression of Arterial Disease and Diabetes; **PPP** = Primary Prevention Project; **PROBE** = prospective, randomized, open with blinded endpoint evaluation; **RCT** = randomized controlled trial; **RR** = relative risk; **TPT** = Thrombosis Prevention Trial; **WHS** = Women's Health Study; [a]studies included in ATT meta-analysis; [b]data taken from ATT; [c]death from coronary heart disease or stroke, nonfatal MI or stroke, or above ankle amputation for critical limb ischemia

therapy in these patients (HR 0.68; 95% CI 0.46 to 0.99; $p = 0.047$).[16]

The actual event rate, 17 per 1,000 patients, fell short of the projected event rate from sample-size calculations (52 per 1,000 Japanese patients with DM).[16] The event rates were based on two antiquated, 1990s epidemiologic studies in Japan[17,18]; since their publication, clinical treatment of CVD risk factors has improved through tighter glucose, blood pressure, and lipid control. The discrepancy between the observed and calculated event rates severely undermined the study's power to reveal a significant effect of aspirin therapy on atherosclerotic events.

JPAD investigators later performed a post-hoc analysis by classifying patients into subgroups based on baseline DM management: insulin ± oral hypoglycemic agent (s) (n = 326), oral hypoglycemic agent(s) (n = 1,750), or diet alone (n = 463).[19] Atherosclerotic events occurred most often in patients receiving insulin (26.6 cases per 1,000 person-years), but aspirin significantly reduced these events only in patients treated with diet alone (HR 0.21; 95% CI 0.05 to 0.64; $p = 0.0069$).[19] Compared with patients receiving insulin, the diet-alone group had statistically significantly higher proportions of baseline CVD risk factors, including hypertension (72% versus 48%), dyslipidemia (56% versus 40%), and older age (mean age, 65 years versus 62 years)[19]. Thus, the benefit of aspirin for primary CVD prevention in this group may have been due to the presence of these risk factors, independent of DM. The insulin-treated group demonstrated a more advanced clinical stage of DM than the diet-alone group as evidenced by a longer median duration of DM (13.0 years versus 3.5 years), poorer glycemic control (HbA1c 8.1% versus 6.7%), and higher prevalence of microvascular complications (>20% versus <10%).[19] Authors proposed that patients with advanced clinical stages of DM might additionally have advanced atherosclerotic disease.[19] These subanalysis results need further validation from more robust trials.

Several recent meta-analyses have evaluated aspirin use in patients with DM since the publishing of both JPAD and POPADAD.[20-22] All in all, even if a significant difference were to be found, the current evidence only points toward a modest reduction in CVD relative risk (~10 to 15%) with aspirin therapy.[6,20-22] The absolute reduction in CVD events, however, depends upon the patient's underlying risk.[23]

Other Considerations

Aspirin resistance, or the incomplete inhibition of platelets by aspirin, is hypothesized to confer treatment failure in patients with DM and account for the reduced clinical efficacy of aspirin. While this theory has not been confirmed, there is a heterogeneous response of platelet function to aspirin.[24] The rate of aspirin resistance is roughly 50% greater for people with DM than those without the disease.[25] The mechanism behind aspirin resistance is likely to be multifactorial (**Table 2**).

Secondly, the ideal dose of aspirin for primary prevention has not been established; the trials discussed in this article used varying dosing schedules of aspirin (100mg every other day to 650mg daily).[8-16] Additionally, the role that aspirin resistance plays in determining optimal dose has not yet been clarified. In order to determine the value of high-dose aspirin, aspirin resistant individuals must first be discovered through platelet response testing. Then, these resistant patients must be randomly assigned to standard aspirin dose or high-dose regimens for comparison.[38] Despite the current uncertainties, low-dose aspirin seems most appropriate based on its pharmacological profile. Aspirin irreversibly inhibits cyclooxygenase (COX; also known as prostaglandin G/H synthase)[39] for the lifetime of the anucleated platelet

Table 2 | Purported mechanisms for aspirin resistance in patients with DM.

Increased rates of TXA_2[26] and isoprostane (prostaglandin-like compounds formed through oxygen free-radical dependent lipid peroxidation)[27] synthesis
Increased sensitivity to collagen- and ADP-based platelet aggregation[28]
Increased platelet adhesion molecules (e.g., glycoprotein IIb-IIIa)[29,30]
Reduced ability to acetylate platelet proteins due to extensive protein glycation[31]
Impaired sensitivity to anti-aggregating effects of nitric oxide[32], prostacyclins[33], and insulin[34]
Accelerated platelet turnover and more rapid recovery of platelet aggregability[35]
Induced COX-2 due to pro-inflammatory vascular alterations[36]
Increased intracellular calcium mobilization resulting in decreased membrane fluidity[37]

(~10 days).[40] Mature platelets predominantly and constitutively express the COX-1 isoform.[41] Low daily doses of aspirin inhibit COX-1 activity, thereby reducing the synthesis of thromboxane A_2 (TXA_2) from arachidonic acid.[42,43] TXA_2 receptor binding on platelets normally triggers an autocrine and paracrine response that leads to downstream activation of platelet aggregation.[44] Endothelial COX-2 activity is suppressed with increasing doses and heightened systemic absorption of aspirin[45]; COX-2 is largely responsible for producing vascular prostacyclins that vasodilate and deter platelet aggregation.[46,47]

The potential reduction in MI and stroke with aspirin therapy must be weighed against adverse side effects, the added burden of taking an additional medication, and the uncertainty of the true benefit in CVD risk reduction. Most concerning, aspirin use bears the associated risk of bleeding, namely intracranial (hemorrhagic stroke) and gastrointestinal (GI). Lanas, et. al discovered a link to non-steroidal anti-inflammatory drug (NSAID) use existed in 80% of reported cases of GI bleeding; 89% of this NSAID use included aspirin.[48] Outside the research setting and in the real world population, aspirin use has accounted for an estimated 5 extra incidents of upper GI bleeding per 1,000 users per year; this number fluctuated paralleling underlying GI risk and could be as high as 10 additional cases per 1,000 in 10% of the population most at risk.[49] The ATT meta-analysis collaborators discovered aspirin significantly increased major GI and other extracranial bleeds (0.10% versus 0.07% per year; RR 1.54; 95% CI 1.30 to 1.82).[6] Simply, 3 additional GI bleeds were expected each year per 10,000 people treated with aspirin. Moreover, hemorrhagic stroke risk was increased by 32% in patients treated with aspirin in the same meta-analysis (116 versus 89 events; 0.01% absolute difference per year; RR 1.32; 95% CI 1.00 to 1.75).[6] ATT discovered that certain risk factors for CVD (e.g., age [per decade], male sex, DM, current smoker, and BP [per 20mmHg]) also increased a patient's risk for intracranial hemorrhage and/or major extracranial bleeds.[6] People with DM, as compared to those without, were at increased risk for major extracranial bleeds (RR 1.55; 95% CI 1.13 to 2.14) but not hemorrhagic stroke (RR 1.74; 95% CI 0.95 to 3.17).[6] Four patients receiving aspirin therapy in the JPAD trial required blood transfusions contrasted by no patients in the control group.[16] Notwithstanding, JPAD found no significant difference between groups in the combined endpoint of severe GI bleed and hemorrhagic stroke.[16] POPADAD similarly did not find a significant difference between aspirin and non-aspirin treatment arms and GI bleeding rate or hemorrhagic stroke.[15]

The effectiveness of prophylactic proton-pump inhibitors (PPIs) against GI bleeding has been established through clinical study.[50] Recently, a cost utility analysis determined cost-effectiveness of PPI add-on therapy in men aged at least 45 years with 10-year CHD risk greater than 10% and an increased risk of GI bleed (risk over 4 per 1,000 per year), but not men with low-average GI bleed risk.[51] While PPI use appears to be a plausible strategy to reduce adverse events and potentially broaden guideline-based recommendations supporting aspirin use, the role of these medications in patients with DM taking aspirin as CVD prevention has yet to be confirmed through clinical study.

Li, et al. performed an analysis to determine the cost-effectiveness of long-term aspirin use in newly diagnosed type II DM patients on the basis of direct medical costs.[52] Therapy was assumed effective in all aspirin users.[52] The investigators used ATT as a base-case scenario whereby coronary events and stroke proportionally decreased by 18% and 5%, respectively.[52] This cost-effectiveness model incorporated the potential side effect of GI bleeding with aspirin use; again, this analysis applied ATT results that GI bleeding occurred at a rate of 0.03 per 100 patients.[52] The authors concluded that lifetime aspirin use beginning at DM diagnosis costs $5,428 for every life year gained and $8,801 for every quality adjusted life year gained (QALY).[52] Considering these values were well below the conventional threshold of $50,000 per QALY, aspirin therapy was deemed cost-effective.

Current Treatment Recommendations

The American Diabetes Association (ADA), the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF) issued a consensus statement in 2009 that outlined aspirin use by patients with DM for primary prevention of CVD.[53] These recommendations were reflected in the ADA's 2010 and 2011 versions of Standards of Medical Care in DM (**Table 3**).[54,55] The ADA changed the strength of their level of evidence from an A rating ("clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered") to a C rating ("supportive evidence from poorly controlled or uncontrolled studies or conflicting evidence with the weight of evidence supporting the recommendation") reflecting the increased level of uncertainty stemming from the aforementioned trials.[54,55]

These recommendations rely on a consistent reduction in relative risk regardless of patient characteristics; thus, patients at high intrinsic risk of CVD would be expected to derive benefit from treatment with aspirin whereas those at low relative risk would likely experi-

Table 3 | 2011 ADA recommendations for antiplatelet therapy.[55]

Consider aspirin therapy (75 to 162mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk > 10%). This includes most men > 50 years of age or women > 60 years of age who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (C)
Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk < 5%, such as in men < 50 and women < 60 years of age with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits. (C)
In patients in these age-groups with multiple other risk factors (e.g., 10-year risk 5 to 10%), clinical judgment is required. (E)
Use aspirin therapy (75 to 162mg/day) as a secondary prevention strategy in those with DM with a history of CVD. (A)
For patients with CVD and documented aspirin allergy, clopidogrel (75mg/day) should be used. (B)
Combination therapy with aspirin (75– 162mg/day) and clopidogrel (75mg/day) is reasonable for up to a year after an acute coronary syndrome. (B)

A = Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered *or* Compelling nonexperimental evidence *or* Supportive evidence from well-conducted randomized controlled trials
that are adequately powered; B = Supportive evidence from well-conducted cohort studies *or* Supportive evidence from well-conducted case-control study; C = Supportive evidence from poorly controlled or uncontrolled studies *or* Conflicting evidence with the weight of evidence supporting the recommendation; E = Expert consensus or clinical experience

ence harm (e.g., bleeding events). The guidelines do not supersede clinical judgment; recommending long-term aspirin therapy values balancing an individual patient's expected benefits against added risks.

The Adult Treatment Panel III (ATP III) Guidelines, published in 2001, assumed that all DM patients exhibited high CVD risk status (CHD risk equivalent) based on their DM diagnosis alone.[56] This method falsely assumes DM is a categorical variable for CVD risk and fails to examine level of glycemic control, DM duration, and other multivariate factors as they relate to risk. The ADA recommends three specific risk assessment calculators to determine cardiovascular risk and, consequently, the decision to treat with aspirin or not: UKPDS Risk Engine (http://www.dtu.ox.ac.uk/riskengine/index.php), ARIC CHD Risk Calculator (http://www.aricnews.net/riskcalc/html/RC1.html), and American Diabetes Association Risk Assessment Tool, Diabetes PHD (http://www.diabetes.org/phd).[56]

Future Studies

Larger, adequately powered trials of patients with DM are needed to better determine whether low-dose aspirin efficaciously affects macrovascular disease. Future studies are additionally necessary to elucidate sex- and age-specific differences in response to aspirin therapy. Further, aspirin therapy for the primary prevention of vascular disease must be considered alongside proven preventative therapies like statins, smoking cessation, and blood pressure management to assess aspirin's potential additive reduction in risk.

Currently, two large clinical trials of aspirin in patients with DM are underway. The first, Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) will examine the effects of combined aspirin (100 mg/day) and simvastatin versus simvastatin alone.[57] Study subjects have been randomly assigned to open-label treatment; endpoint evaluation will be blinded.[57] Eligible patients include patients with DM aged at least 50 years with persistent elevated LDL (> 100mg/dL after 3 months of lifestyle modifications) or current treatment with statin therapy.[57] ACCEPT-D will study the incidence of major vascular events, a combined primary endpoint including cardiovascular death, non-fatal MI, non-fatal stroke, or hospital admission for cardiovascular causes (including acute coronary syndrome, unplanned revascularization procedures, and peripheral vascular disease).[57] The study aims to enroll 5,170 patients in order to observe 515 events, a 25% reduction in the risk of cardiovascular events with α level 0.05 and 90% power.[57]

The second large trial, a University of Oxford-based randomized 2x2 factorial study, A Study of Cardiovascular Events in Diabetes (ASCEND), began enrolling patients with DM without pre-existing arterial disease in March 2005 to determine the benefits of aspirin and/or omega-3 fatty acids on cardiovascular events.[58] By study completion, ASCEND researchers hope to enroll 10,000 patients with a 5 year treatment period in order to detect a 20% proportional reduction in the combined endpoint of non-fatal MI, non-fatal stroke, or vascular death (excluding

intracranial hemorrhage).[58]

Study completion for ACCEPT-D and ASCEND is anticipated for March 2015 and December 2013, respectively.[59,60]

Summary

Recent clinical studies of aspirin use by patients with DM for the primary prevention of CVD have given way to an updated set of recommendations from the ADA, AHA, and ACCF. These changes reflect the increased uncertainty of aspirin's effectiveness as manifested in the POPADAD and JPAD trials. Besides efficacy, adverse effects associated with aspirin therapy (e.g., bleeding) and the potential for aspirin resistance by patients with DM must be considered before making broad recommendations. In summary, sufficient evidence exists to support aspirin use in patients with DM at high estimated CVD risk. Results of future studies should further clarify the role of aspirin and strengthen current recommendations.

References

1. Fox CS, Coady S, Sorlie PD, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. *Circulation* 2007;115(12):1544-1550.
2. Miettinen H, Lehto S, Salomaa V, et al. Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care* 1998;21:69-75.
3. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-234.
4. Centers for Disease Control and Prevention. National Diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
6. Antithrombotic Trialists' Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-1860.
7. US Preventive Services Task Force: aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009;150:396-404.
8. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293-1304.
9. Sacco M, Pellegrini F, Roncaglioni MC, et al. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 2003; 26:3264-3272.
10. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-1762.
11. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998;351:233-241.
12. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989;321:129-135.
13. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *BMJ* 1988;296:313-316.
14. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. *JAMA* 1992;268:1292-1300.
15. Belch J, MacCuish A, Campbell I, et al. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840.
16. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134-2141.
17. Fujishima M, Kiyohara Y, Kato I, et al. Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes* 1996;45:S14-S16.
18. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. *Diabetes Care* 1999;22:920-924.
19. Okada S, Morimoto T, Ogawa H, et al. Aspirin for primary prevention of atherosclerotic events in diabetes manage-

ment: a subanalysis of the JPAD trial. *Diabetes Care* 2011;34:1277-1283.
20. De Berardis G, Sacco M, Strippoli GF, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* 2009;339:b4531.
21. Zhang C, Sun A, Zhang P, et al. aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Diabetes Res Clin Pract* 2010;87(2):211-218.
22. Stavrakis S, Stoner JA, Azar M, et al. Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis. *Am J Med Sci* 2011;341 (1):1-9.
23. Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* 2010;33:1395-1402.
24. Watala C, Golanski J, Pluta J, et al. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin)-its relation to metabolic control. *Thromb Res* 2004;113: 101-113.
25. Eikelboom JW, Hirsh J, Weitz JI, et al. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002;105:1650-1655.
26. Davì G, Catalano I, Averna M, et al. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med* 1990;322:1769-1774.
27. Davì, G. et al. Platelet activation in obese women: role of inflammation and oxidant stress. *JAMA* 2002;288:2008-2014.
28. DiChiara J, Bliden KP, Tantry US, et al. The effect of aspirin dosing on platelet function in diabetic and nondiabetic patients: an analysis from the aspirin- induced platelet effect (ASPECT) study. *Diabetes* 2007;56:3014-3019.
29. Tschoepe D, Roesen P, Kaufmann L, et al. Evidence for abnormal platelet glycoprotein expression in diabetes mellitus. *Eur J Clin Invest* 1990;20:166-170.
30. Tschoepe D, Rauch U, Schwippert B. Platelet-leukocyte-cross-talk in diabetes mellitus. *Horm Metab Res* 1997;29:631-635.
31. Watala C, Pluta J, Golanski J, et al. Increased protein glycation in diabetes mellitus is associated with decreased aspirin-mediated protein acetylation and reduced sensitivity of blood platelets to aspirin. *J Mol Med* 2005;83(2):148-158.
32. Rajendran S, Chirkov YY. Platelet hyperaggregability: impaired responsiveness to nitric oxide ("platelet NO resistance") as a therapeutic target. *Cardiovasc Drugs Ther* 2008;22(3):193-203.
33. Akai T, Naka K, Okuda K, et al. Decreased sensitivity of platelets to prostacyclin in patients with diabetes mellitus. *Horm Metab Res* 1983;15(11):523-526.
34. Trovati M, Anfossi G. Mechanisms involved in platelet hyperactivation and platelet-endothelium interrelationships in diabetes mellitus. *Curr Diab Rep* 2002;2:316-322.
35. DiMinno G, Silver MJ, Cerbone AM, et al. Trial of repeated low-dose aspirin in diabetic angiopathy. *Blood* 1986;68:886-891.
36. Patrignani P. Aspirin insensitive eicosanoid biosynthesis in cardiovascular disease. *Thromb Res* 2003;110:281-286.
37. Watala C, Boncer M, Golanski J, et al. Platelet membrane lipid fluidity and intraplatelet clcium mobilization in type 2 diabetes. *Eur J Haematol* 1998;61:319-326.
38. Pignone M, Willliams CD. Aspirin for primary prevention of cardiovascular disease in diabetes mellitus. *Nat Rev Endocrinol* 2010;6:619-628.
39. FitzGerald GA, Pedersen AK, Patrono C. Analysis of prostacyclin and thromboxane biosynthesis in cardiovascular disease. *Circulation* 1983;67:1174-1177.
40. Roth GJ, Stanford N, Majerus PW. Acetylation of prostaglandin synthase by aspirin. *Proc Natl Acad Sci U S A* 1975;72:3073-3076.
41. Rocca B, Secchiero P, Ciabattoni G, et al. Cyclooxygenase-2 expression is induced during human megakaryopoiesis and characterizes newly formed platelets. *Proc Natl Acad Sci U S A* 2002;99(11):7634-7639.
42. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest* 1982;69 (6):1366-1372.
43. FitzGerald GA, Oates JA, Hawiger J, et al. Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man. *J Clin Invest* 1983;71:678-688.
44. FitzGerald GA. Mechanisms of platelet activation: thromboxane A_2 as an amplifying signal for other agonists. *Am J Cardiol* 1991;68:11B-5B.
45. Cipollone F, Patrignani P, Greco A, et al. Differential suppression of thromboxane biosynthesis by indobufen and aspirin in patients with unstable angina. *Circulation* 1997;96:1109-1116.
46. Patrono C, García Rodríguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;353:2373-2383.
47. Caughey GE, Cleland LG, Penglis PS, et al. Roles of cyclooxygenase (COX)-1 and COX-2 in prostanoid production by human endothelial cells: Selective up-regulation of prostacyclin synthesis by COX-2. *J Immunol* 2001;167:2831-2838.
48. Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding. *Gastroenterology* 1992;103:862-869.
49. Hernández-Díaz S, García Rodríguez LA. Cardioprotective aspirin users and their excess risk of upper gastrointestinal complications. *BMC Med* 2006;4:22.
50. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-

term low-dose aspirin use. *N Engl J Med* 2002;346:2033–2038.
51. Earnshaw SR, Scheiman J, Fendrick AM, et al. Cost-utility of aspirin and proton pump inhibitors for primary prevention. *Arch Intern Med* 2011;171(3):218-225.
52. Li R, Zhang P, Barker LE, Hoerger TJ. Cost-effectiveness of aspirin use among persons with newly diagnosed type 2 diabetes. *Diabetes Care* 2010;33:1193-1199.
53. Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* 2010;33:1395-1402.
54. American Diabetes Association. Standards of medical care in diabetes: 2010. *Diabetes Care* 2010;33(1):S11-S61.
55. American Diabetes Association. Standards of medical care in diabetes: 2011. *Diabetes Care* 2011;34(1):S11-S61.
56. Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497.
57. De Berardis G, Sacco M, Evangelista V, et al. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. *Trials* 2007;8:21.
58. British Heart Foundation. ASCEND: A Study of Cardiovascular Events in Diabetes. Available at http://www.ctsu.ox.ac.uk/ascend/. Accessed 8 May 2011.
59. Current Controlled Trials Ltd. ISRCTN48110081 Aspirin and simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes. Available at http://controlled-trials.com/ISRCTN48110081/48110081. Accessed 8 May 2011.
60. Current Controlled Trials Ltd. ISRCTN60635500 A Study of Cardiovascular Events In Diabetes. Available at http://www.controlled-trials.com/ISRCTN60635500. Access 8 May 2011.

Drug Updates

Rivaroxaban oral tablets (Xarelto®) - Janssen Pharmaceuticals

On July 1, 2011 the FDA approved rivaroxaban, an oral factor Xa inhibitor, for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. Rivaroxaban is dosed at 10 mg daily, with or without food, for 12 days following knee surgery and 35 days following hip surgery. Rivaroxaban was as effective as enoxaparin 40 mg SC daily in reducing the risk for DVT and PE following hip (RECORD-1 and –2 studies) and knee (RECORD-3 study) replacement surgery in clinical trials. The most common side effect is bleeding, occurring in up to 6% of patients. Bleeding can range from minor to severe and/or fatal. It is not recommended to be used in patients with significantly reduced renal function (CrCl < 30 mL/min), and use is cautioned in patients with a CrCl of 30-50 mL/min. It should also be avoided in patients with moderate-to-severe hepatic impairment (Child-Pugh class B or C). Rivaroxaban is a substrate for p-glycoprotein (P-gp) and CYP 3A4. Therefore, concomitant use with agents that are combined P-gp and strong CYP 3A4 inducers should be avoided. If concomitant use is unavoidable, a dose increase to 20 mg daily should be considered. Rivaroxaban is currently undergoing clinical studies for use in acute coronary syndromes, acute treatment of DVT and PE, as well as stroke prevention in atrial fibrillation.

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